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NOVARTIS VACCINES AND DIAGNOSTICS INC.

INTELLECTUAL PROPERTY R338

P.O. BOX 8097

Emeryville, CA 94662-8097

EXAMINER

RAGHU, GANAPATHIRAM

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application Status

In response to the Office Action mailed on 07/11/2007, applicants' filed a response on 01/11/2008. Said response amended claims 3, 4, 6, 9 and 11 and canceled claims 8, 12, 13 and 15. Thus claims 1-7, 9, 11 and 14 are pending in this application. Claim 14 remains withdrawn as being drawn to non-elected invention and claims 1-7, 9 and 11 are now under consideration.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Claim Objections

Claim 4 objected to because of the following informalities: Claim 4 recites non-elected subject matter such as SEQ ID NOs: 2 and 3. Appropriate correction is required.

Maintained-Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Maintained-Enablement

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mutant *Neisseria meningitidis* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitidis* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), does not reasonably provide enablement for any mutant *Neisseria meningitidis* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 5-7, 9 and 11 are so broad as to encompass for any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino

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acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this case the disclosure is limited to an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claims, i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such

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modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The specification does not enable the full scope of claims 1-3, 5-7, 9 and 11, because the specification does not establish: **(A)** mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the structure of all polypeptides with desired activity i.e., reduced or eliminated ADP-ribosyltransferase activity and as an immunogen; **(B)** the general tolerance of the polypeptide to modification and extent of such tolerance; **(C)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(D)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides and encoding polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

In support of their request that said rejection be withdrawn, applicants' provide the following arguments:

Applicants' have enabled Glu to Asp substitutions at any Glu-109, Glu-111 or Glu-120... even if one skilled in the art could not predict that any of the other eighteen residues would provide the claimed function, screening such would be an entirely routine procedure... which requires mere fifty-seven mutants. However, examiner maintains the rejection and the reason for the examiner's position is given below.

Reply: At the outset examiner would like to point out that applicants' have construed that the amendments to claims limits the claims only to what is disclosed in the specification and the crux of the applicants' argument is based on this conception i. e., the mutation encompasses only

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the catalytic residues of Glu-109, Glu-111 or Glu-120 of SEQ ID NO: 1. However, examiner would like to reiterate that the conception/belief of the applicant is not correct. Amended claims as written when given the broadest reasonable interpretation reads on any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen i.e., any random mutants of SEQ ID NO: 1 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Furthermore, the specification only discloses three specific mutants (SEQ ID NO: 2, 3 & 4) comprising the full-length sequence of SEQ ID NO: 1 having reduced or eliminated ADP ribosyltransferase and or NAD-glycohydrolase activity as compared to the wild-type enzyme and said mutants to be immunogenic. However, the specification has not provided structure-function relationship (able to elicit protective antibodies) i. e., any other random mutant of SEQ ID NO:1 or any other fragment of SEQ ID NO: 1 of any length wherein said fragment includes one or more amino acids Glu-109, Glu-11 or Glu-120 or said residues substituted with any other residue in said ribosylating protein and being immunogenic. Therefore, the specification does not provide support for the full scope and breadth of the claims even following the amendments to claims and examiner continues to hold the position the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Maintained-Written Description

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-7, 9 and 11, as interpreted, are directed to a genus of polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that “A written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as by structure, formula, [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials”. As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no structure correlated to associated function (eliciting protective antibodies) recited in claims with regard to the members of the genus polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or

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Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. While the specification in the instant application discloses the structure; an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), it fails to provide any information as to the structure associated with function for the genus of polypeptides claimed i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, with no structural limitations. The lack of description of any additional mutants from any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that said rejection be withdrawn, applicants' have provided the following argument. Applicants' have disclosed more than sufficient correlation between structure and function... crystal structures are known... catalytic residues are identified and thus structure and function relationship is completely clear. However, examiner maintains the rejection and the reason for the examiner's position is given below.

Reply: Applicants' arguments are not persuasive because claims as written is not limited to only the catalytic residues of Glu-109, Glu-111 or Glu-120 of SEQ ID NO: 1 and as indicated above in the enablement rejection, claims when given the broadest reasonable interpretation reads on any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Based on this interpretation and lack of description of any additional mutants and their structure-function relationship i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme or any protein comprising fragments of said mutant wherein said polypeptides or the fragments of said polypeptides have reduced or eliminated ADP ribosyltransferase and/or NAD-glycohydrolase activity and use of said mutants as an immunogen (eliciting protective antibodies) by any relevant, identifying characteristics or properties, one of

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skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Maintained-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Masignani et al., (WO 02/079242 A2, publication date 10/10/2002) when given the broadest interpretation. Claims 1-3, 5-9 and 11 are directed to any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution at one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen or mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). Masignani et al., (*supra*) have disclosed a mutant *Neisseria meningitides* ADP-ribosylating enzyme comprising substitution of Glu-109 or Glu-111 or Glu-120 with Asp of *Neisseria meningitides* wild-type ADP-ribosylating enzyme of SEQ ID NO: 1 and use of said mutant ADP-ribosylating enzyme as an immunogen (pages 2-5 and

especially Table 1 preferred site of mutations and replacement residue). Therefore the reference of Massignani et al., anticipates claims 1-3, 5-9 and 11 of the present invention.

In support of their request that said rejection be withdrawn, applicants' provide the following arguments:

(A) "An application for patent, published under Section 122(b), by another filed in the United States before the invention by the applicant ..."

(B) "Applicants' are in the process of determining whether Rino Rappuoli should be added in light of the currently pending scope ..."

However, examiner maintains the rejection and the reason for the examiner's position is given below.

Reply: Applicants' arguments are not persuasive because *35 USC § 102 (e)* states the reference can be U.S. Patents, Published U.S. patent applications and WIPO/PCT International applications: Filed after November 29, 2000, designating the U. S., and published in English. Therefore, the cited rejection is valid as the cited reference is deemed to be by another. The cited reference is also applied for rejection under *35 USC § 102 (a)*, as the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claim 4 objected to because of the following informalities: Claim 4 recites non-elected subject matter such as SEQ ID NOs: 2 and 3.

2. Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, for enablement and written description.

3. Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Massignani et al., (WO 02/079242 A2, publication date 10/10/2002).

Conclusion

None of the claims are allowable. Claims 1-7, 9 and 11 are objected/rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Applicants must respond to the objections/rejections in each of the sections in this Office Action to be fully responsive for prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

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will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652
Mar. 03, 2008.

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652